

# Mechanisms of ART-free virus control of SHIV with AAV gene therapy delivery of eCD4Ig

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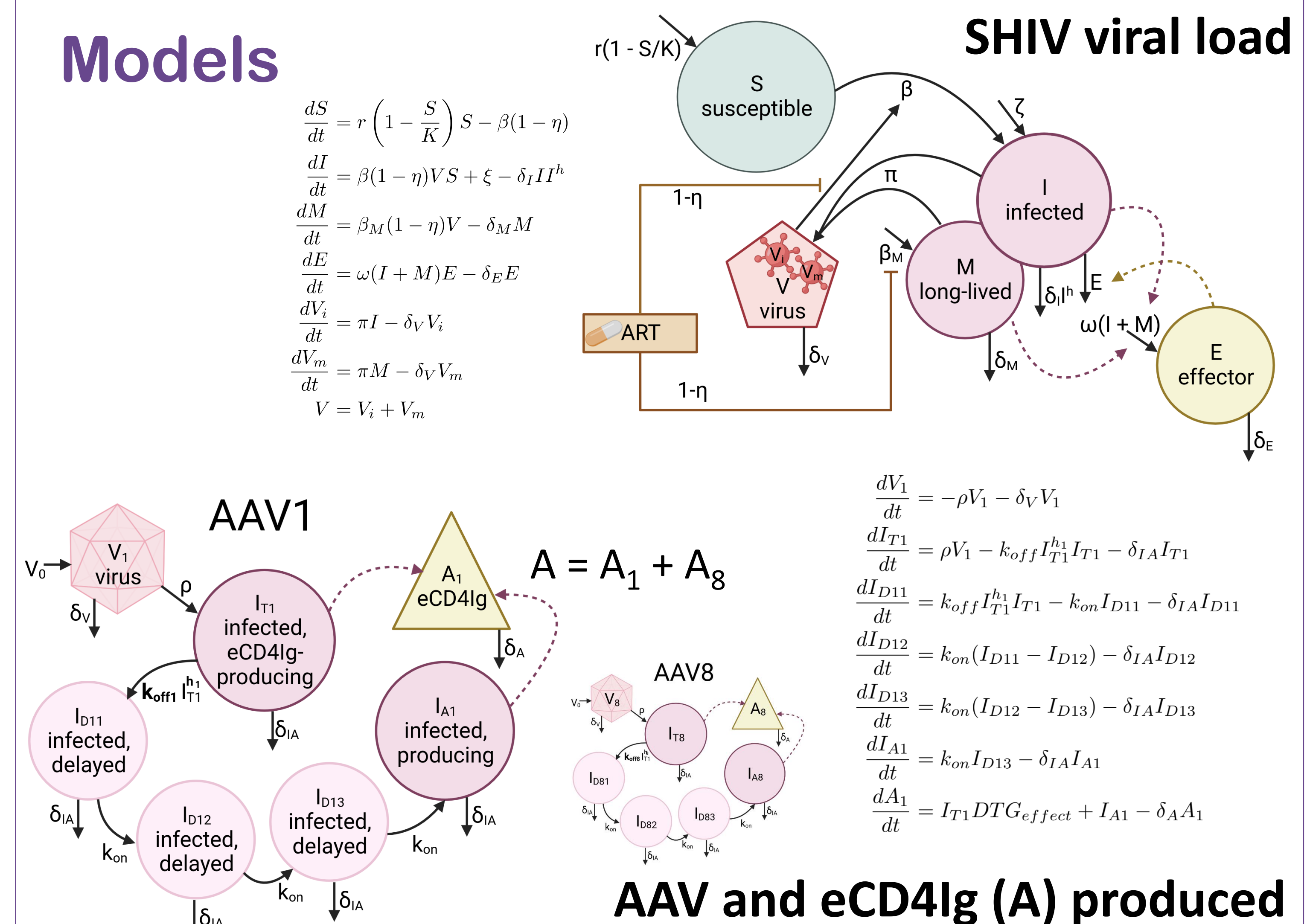
## Introduction

One **gene-based approach for HIV cure** is Adeno-associated virus (AAV) vectors encoding the **antibody-like peptide eCD4Ig** [1]. This **potent entry inhibitor** neutralizes a greater breadth of HIV isolates in-vitro than all anti-HIV broadly neutralizing antibodies discovered to date [2], and injection of AAV vectors encoding eCD4Ig may be protective from challenge with simian-HIV (SHIV) [3-5]. Ongoing pilot studies examine if **AAV-delivered eCD4Ig** can induce antiretroviral therapy **ART-free virus control** in SHIV-infected primates after ART interruption.

### Objectives:

1. Develop models which recapitulate the complex observed dynamics of AAV viral loads, eCD4Ig levels and downstream effects on HIV viral load.
2. Use the model to explore conditions for ART-free virus remission.

## Models

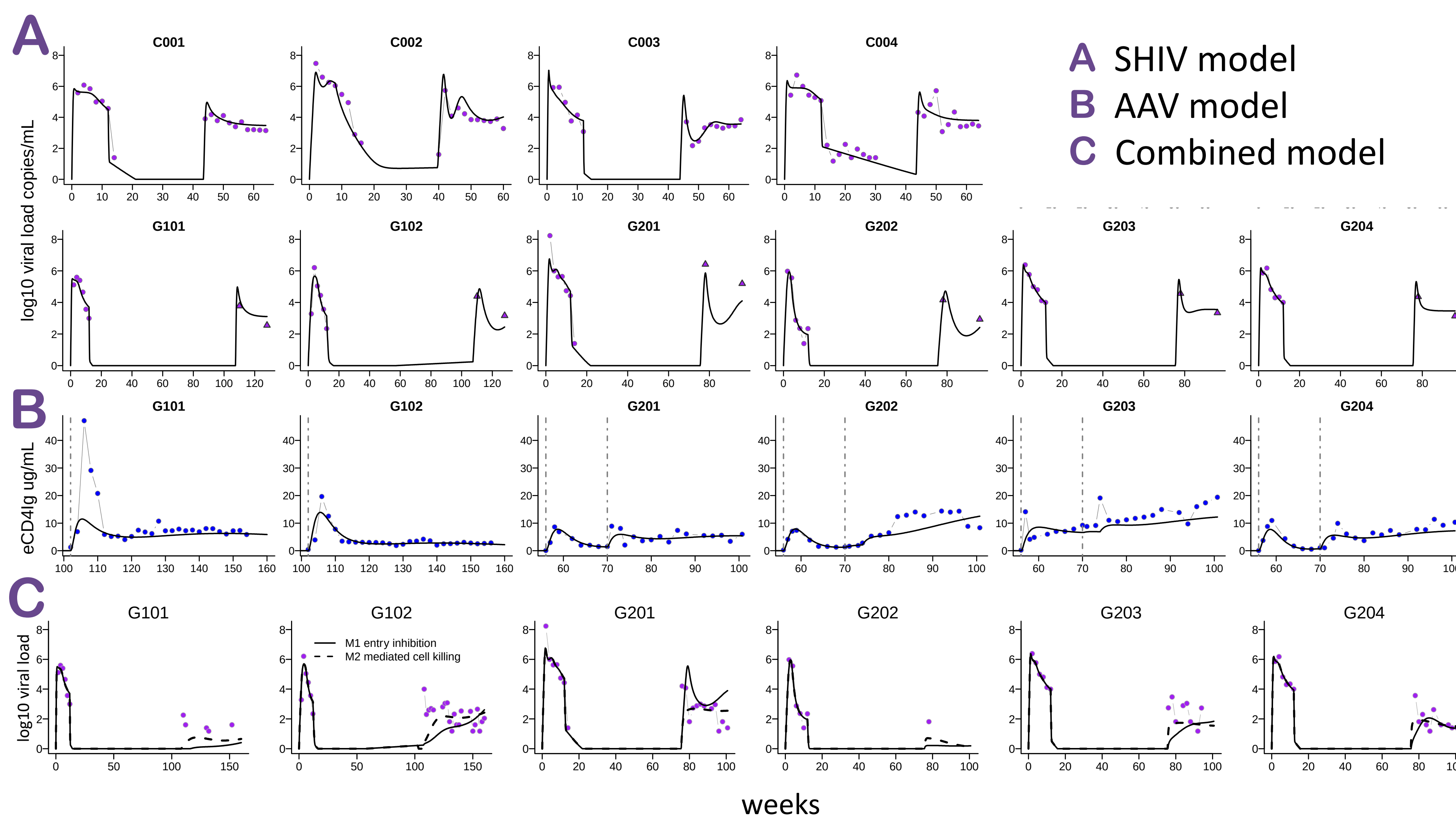


## Experimental design

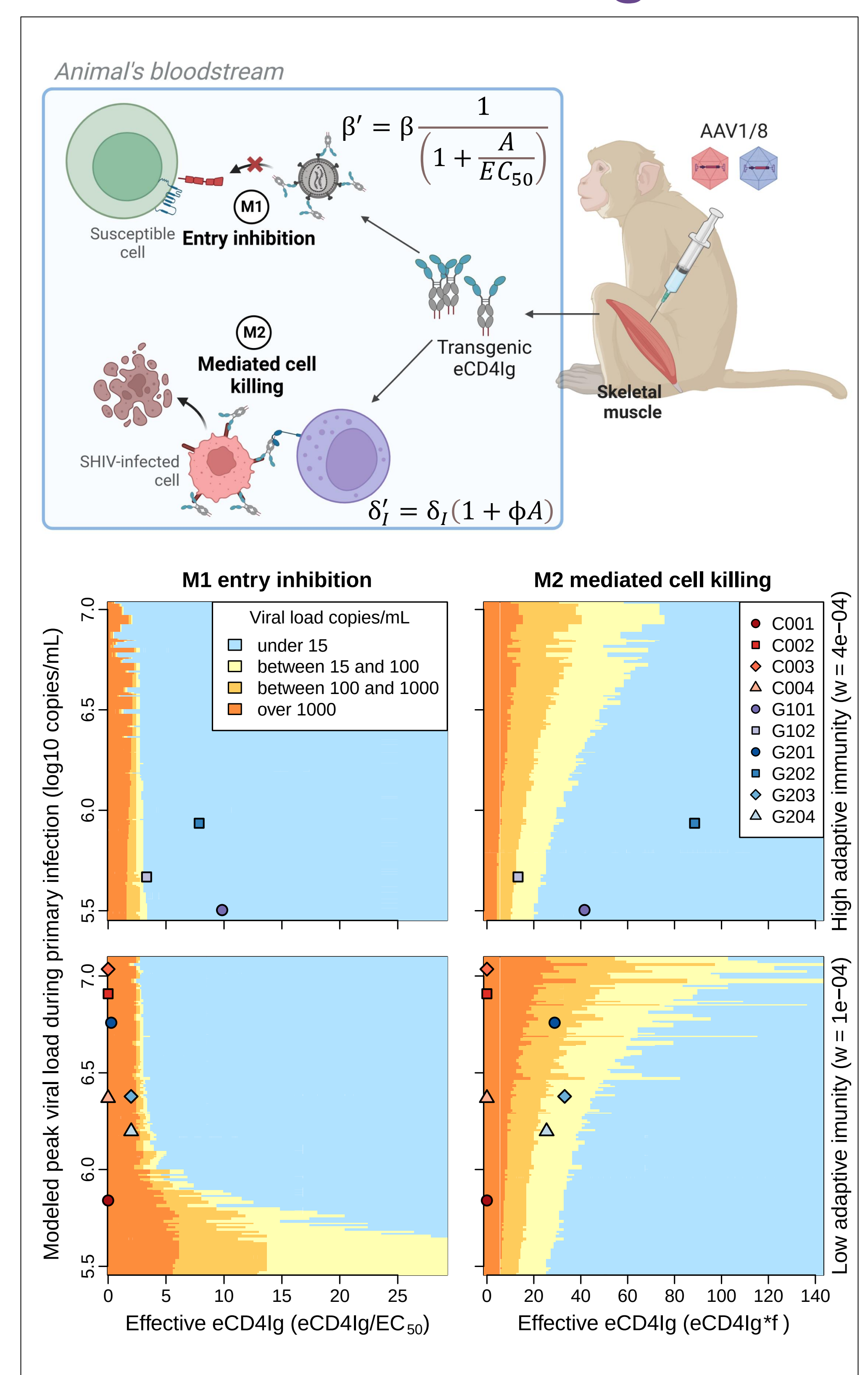
**10 rhesus macaques** infected with SHIV-AD8 given **ART 12 weeks post-infection** (tenofovir, emtricitabine, and dolutegravir)

- **Control** (n = 4) **stopped ART after 30 weeks**
- **Group 1** (n = 2) given **AAV1- and AAV8-vectors after 22 and 92 weeks** of starting ART
- **Group 2** (n = 4) given **AAV8- and AAV1-vectors after 44 and 58 weeks** of starting ART

## Model fits



## Mechanism of eCD4Ig action



## Discussion

- Our mathematical model results support that **AAV-delivered eCD4Ig could achieve post-treatment control of HIV** following ATI.
- We cannot confidently discriminate the eCD4Ig mechanism, with implications for balance of factors leading to immune control and the amount of eCD4Ig needed for post-treatment control. While **our model favors enhanced cell-mediated killing** over neutralization via BIC criteria, our **prior modeling suggested that neutralization** was the more likely mechanism.
- These results suggest that **the determinants of post-treatment control are multi-factorial and extraordinarily complex**, including eCD4 level, eCD4 potency, eCD4 mechanism, strength of the innate immune response, and strength of the acquired immune response. However, a **sufficient level of eCD4Ig is predicted to achieve post-treatment control regardless**, and **eCD4Ig level and potency are the two most critical determinants**.

## References:

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2. Fetzer I et al. eCD4-Ig Variants That More Potently Neutralize HIV-1. J Virol. 2018 May 29;92(12):e02011-17.
3. Gardner MR et al. AAV-expressed eCD4-Ig provides durable protection from multiple SHIV challenges. Nature. 2015 Mar 5;519(7541):87-91.
4. Gardner MR et al. AAV-delivered eCD4-Ig protects rhesus macaques from high-dose SIVmac239 challenges. Sci Transl Med. 2019 Jul 24;11(502):eaau5409
5. Goyal A et al. Estimation of the in vivo neutralization potency of eCD4Ig and conditions for AAV-mediated production for SHIV long-term remission. Sci Adv. 2022 Jan 14;8(2):eabj5666.